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Original research article

Treatment and its side effects in ANCA-associated vasculitides – Study based on POLVAS registry data

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ABSTRACT

Purpose: The aim of this study is to present the treatment modalities and associated side effects in a Polish nation-wide ANCA-associated vasculitides (AAV) patients' cohort.

Materials and methods: Retrospective analysis of patients diagnosed with AAV between 1990 and 2016, included in the POLVAS registry was performed. Standard descriptive statistic methods were used with an emphasis on the treatment modalities.

Results: There were 625 patients diagnosed with AAV included in this study: 417 cases of granulomatosis with polyangiitis (GPA; 66.7%), 106 cases of microscopic polyangiitis (MPA; 17.0%) and 102 cases of eosinophilic granulomatosis with polyangiitis (EGPA; 16.3%). The mean age at the date of diagnosis was 50.4 (± 15.7) years and the median observational period amounted to 4.0 (2.0–8.0) years.

Glucocorticosteroids (GCs) were the medicaments most frequently used for remission induction (593/622; 95.3%), followed by cyclophosphamide (487/622; 78.3%), rituximab (44/622; 7.1%), and methotrexate (39/622; 6.3%). GCs were also most frequently administered for maintenance therapy (499/592; 84.3%), followed by azathioprine (224/592; 37.8%), methotrexate (136/592; 23.0%) and mycophenolate mofetil (99/592; 16.7%). The median cumulative doses of cyclophosphamide and rituximab equalled 7.99 g (4.18–14.0) and 2000 mg (1500–2800), respectively. The most commonly observed adverse events included: infections - 214/551 cases (38.8%), which were associated with the time of observation (OR = 1.05; 95% CI 1.01–1.10), the use

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of GCs intravenous pulses (OR = 2.76; 95% CI 1.68–4.54) and need for haemodialysis (OR = 1.73; 95% CI 1.10–2.71).
Conclusions: Polish patients with AAV were predominantly treated according to appropriate guidelines. The most frequent adverse events were typical for usually administered immunosuppressive treatment.

1. Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of rare, autoimmune diseases, affecting predominantly small vessels. According to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, the group of AAV consists of three distinct entities, namely, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. The annual incidence of these diseases is estimated to be 4.9–10.2 per million for GPA, 2.7–11.6 per million for MPA and 0.5–4.2 per million for EGPA [2]. Since glucocorticosteroids and the other immunosuppressive drugs were introduced for the management of AAV, the outcomes for the sufferers have significantly improved and these disorders have changed their status from rapidly progressive and inevitably fatal conditions to chronic, relapsing diseases, if early diagnosed and properly treated. Despite this undeniable progress, the optimal treatment regimens are still being discussed and revised, with relevant difficulties related to the rarity of the diseases and scarcity of the large clinical trials. Moreover, due to generally better prognosis, the short and long-term complications of the treatment have become an important factor influencing mortality and morbidity. For these reasons, search for optimal treatment regimens, tailored for distinct subsets of AAV, and careful monitoring of possible side effects are warranted.

1.1. POLVAS

Due to the rarity of AAV, it is impossible for a single centre to design and pursue prospective, randomized, clinical trials regarding management. Therefore, multi-center databases – called Rare Diseases Registries (RDRs) - are recommended by the European Union Committee of Experts on Rare Diseases (EUCERD) [3].In 2014, the Consortium of the Polish Vasculitis Registry (POLVAS) was established [4], consisting of both retrospective and prospective branches of the registry. The aim of this study is to present the treatment modalities and associated side effects among the patients of Polish population with AAV registered in the retrospective part of POLVAS database.

2. Material and methods

2.1. Methods

In the retrospective part of POLVAS database, 625 cases of AAV were included, encompassing patients diagnosed with AAV from 1990 to 2016, who stayed under the care of POLVAS affiliated centers. The POLVAS registry structure was described elsewhere [4,5]. The medical history of the participants was analysed retrospectively and the data regarding treatment protocols, adverse effects and complications were collected using electronic questionnaires. All cases of AAV available in the documentation gathered in POLVAS affiliated centers were included into retrospective part of POLVAS.

The vasculitides diagnoses were made according to the American College of Rheumatology (ACR) classification and 2012 Revised International Chapel Hill Consensus criteria [1,6].

Additionally, AAV patients were subdivided into 3 subgroups according to the time when definite diagnosis was established, i.e. 1) before 2004, 2) between 2004 and 2010, and 3) after 2010). The division was based on the time of publishing the results of breakthrough researches - CYCAZAREM in 2003, and RAVE and RITUXIVAS both in 2010 [7–9] – which significantly influenced treatment regimens in AAV.

2.2. Ethical issues

The study was carried out in accordance with The Code of Ethics of the World Medical Association (1964 Declaration of Helsinki). The study protocol was approved by Jagiellonian University Bioethics Committee (Poland), approval No. 122.6120.25.2016. All POLVAS sites acquired local ethics committee approval before starting the recruitment.

2.3. Statistical analysis

Standard descriptive statistics were used. Normal distribution of variables was checked by Shapiro-Wilk test, and Levene's test served to assess homogeneity of variances. To compare the studied groups $\chi 2$ test (with Yates correction if needed) was used. Univariate ANOVA with post-hoc test was performed for comparisons of normally distributed variables and Kruskal-Wallis test with pairwise comparisons or Mann-Whitney *U* test were carried out for comparisons of non-normally distributed variables. Binary logistic regression was used for assessment of the odds ratios of distinct variables. The p-value < 0.05 was assumed as statistically significant, modified with Bonferroni correction when multiple comparisons were performed. Calculations were performed with StatSoft Statistica 13 software (StatSoft®, Tulsa, OK, USA) and SPSS Statistics (IBM®, USA).

Table 1
Basic description of the group.

	All	GPA	MPA	EGPA	p-value[a]		
No. of cases (N)	625	417 (66.7%)	106 (17.0%)	102 (16.3%)	–		
Men	298 (47.7%)	210 (50.4%)	54 (50.9%)	34 (33.3%)	0.1009		
Mean age (years)	50.4 ± 15.7	49.0 ± 15.3	61.5 ± 13.8	44.8 ± 14.4	**< 0.0001**		
Median observation (years)	4.0 (2.0–8.0)	5.0 (2.0–8.0)	2.0 (1.0–4.0)	5.5 (3.0–10.0)	**0.0206**		
Deaths	56 (8.96%)	42 (10.07%)	13 (12.26%)	1 (0.98%)	GPA vs MPA 0.5112	GPA vs EGPA **0.0053**	MPA vs EGPA **0.0030**
Cases with at least one relapse[b]	340 (54.9%)	243 (58.8%)	27 (25.5%)	70 (70.0%)	GPA vs MPA **< 0.0001**	GPA vs EGPA **0.0400**	MPA vs EGPA **< 0.0001**

Statistically significant p-values are **bolded**.
[a] P-value is evaluated for the group of all cases. $\chi 2$ and Kruskal-Wallis tests were used (assumed level of significance = 0.05).
[b] There were 6 cases with no available data in this analysis – 4 cases of GPA and 2 cases of EGPA.

3. Results

3.1. Group description

Six hundred and twenty-five patients were qualified to this study (all patients included in the retrospective POLVAS database). Among them, there were 417 cases of GPA (66.7%), 106 cases of MPA (17.0%) and 102 cases of EGPA (16.3%). The median time of observation (defined as the difference between the date of inclusion to the database and the date of establishment of the diagnosis) equalled 4.0 (2.0–8.0) years with the shortest observation in MPA (2.0; 1.0–4.0 years). Basic demographic characteristics are presented in Table 1. There were 469 ANCA positive patients, 62 ANCA negative patients (mostly in EGPA group) and 94 had unknown ANCA status. Detailed immunological profile of included subjects is presented in the Supplementary Table s1.

3.2. Treatment - remission induction

Remission induction treatment was defined as the therapy used either until remission achievement or during the first six months of treatment, if the remission was not achieved. Glucocorticosteroids (GCs) were the drugs most frequently used for remission induction therapy. There was no statistical difference in GCs use between AAV groups. GCs pulses, defined as administering 500 mg or more methylprednisolone (or other GCs in equivalent dose) in a single intravenous (i.v.) infusion were used in 378 cases (378/513; 73.7%). Patients with GPA, as well as those with MPA were administered GCs pulses more frequently than patients diagnosed with EGPA (283/368, 76.9% vs. 19/48, 39.6%; $p < 0.0001$ and 76/97, 78.4% vs. 19/48, 39.6%; $p < 0.0001$, respectively).

The second immunosuppressive agent most frequently used for remission induction was cyclophosphamide (487 cases; 78.3%), followed by rituximab (58 cases; 9.3%). Cyclophosphamide was used significantly more often in GPA and MPA than in EGPA (355/414, 85.7% vs. 44/102, 43.1%; $p < 0.0001$ and 88/106, 83.0% vs. 44/102, 43.1%; $p < 0.0001$, respectively). Rituximab was used more frequently in GPA than in MPA (53/414, 12.8% vs. 5/106, 4.7%; $p < 0.02$). None of the patients with EGPA received rituximab for remission induction treatment.

On the contrary, the use of methotrexate, as well as azathioprine was significantly more frequent in EGPA comparing to GPA and to MPA (methotrexate: 16/102, 15.7% vs. 22/414, 5.3%; $p = 0.0003$ and 16/102, 15.7% vs. 1/106, 0.9%; $p = 0.0003$, respectively; azathioprine: 14/102, 13.7% vs. 14/414, 3.4%; $p < 0.0001$ and 14/102, 13.7% vs. 2/106, 1.9%; $p = 0.0033$, respectively). More detailed information is presented in Table 2.

3.3. Renal replacement therapy

Haemodialysis was required in 134 (21.9%) of all AAV cases during the analysed period. Ninety one patients (14.8%) required haemodialysis permanently while 43 (7.0%) were hemodialyzed temporarily during the course of the disease. None of EGPA patients needed renal replacement therapy. MPA patients predominated among patients requiring dialysis (47/106, 44.3% vs. 87/405, 21.5%; $p < 0.001$). The details are presented in Table 3. Among the patients who needed renal replacement therapy, the only significant difference between temporarily and permanently hemodialyzed was the age ($p = 0.002$; medians - 60 and 54 years, respectively.) The details are presented in the Supplementary Table s2.

3.4. Treatment – maintenance therapy

Maintenance treatment was defined as the therapy after remission achievement or after the first 6 months of treatment, if the remission was not achieved. GCs were used for maintenance therapy in 499 cases (84.3%). In most cases with available data, GCs were used for the whole time of observation (median = 100.0% (70.0–100.0)).Other immunosuppressive drugs used frequently for maintenance therapy were: azathioprine (224 cases; 37.8%), methotrexate (136 cases; 23.0%), mycophenolate mofetil (99 cases; 16.7%) and cyclophosphamide (70 cases; 11.8%). No maintenance treatment was used in 36 cases (6.1%). Azathioprine was administered more frequently to GPA patients than to MPA (162/402, 40.3% vs. 23/103, 22.3%; $p = 0.0007$) and also significantly more frequently in EGPA as compared to MPA (39/87, 44.8% vs. 23/103, 22.3%; $p = 0.0010$). Similarly, methotrexate was used more frequently in GPA comparing with MPA (104/402, 25.9% vs. 8/103, 7.8%; $p = 0.0001$) and again administered more frequently in EGPA as compared with MPA (24/87, 27.6% vs. 8/103, 7.8%; $p = 0.0003$). The details are presented in Table 4.

Table 2
Treatment use for remission induction.

	All	GPA	MPA	EGPA	GPA/MPA	GPA/EGPA	MPA/EGPA
GCs use (all forms of administration) #	593 (95.3%)	388 (93.7%)	104 (98.1%)	101 (99.0%)	0.1219	0.0568	0.9732
GCs only orally	123 (19.8%)	75 (18.1%)	15 (14.2%)	33 (32.4%)	0.3356	**0.0015**	**0.0018**
GCs only intravenously	187 (30.1%)	124 (30.0%)	60 (56.6%)	3 (2.9%)	**< 0.0001**	**< 0.0001**	**< 0.0001**
GCs both orally and intravenously	281 (45.2%)	187 (45.2%)	29 (27.4%)	65 (63.7%)	**0.0009**	**0.0008**	**< 0.0001**
GCs without any other immunosuppressive drug	78 (12.5%)	27 (6.5%)	15 (14.2%)	36 (35.3%)	**0.0101**	**< 0.0001**	**0.0004**
GCs pulses used (at least 1)	378† (73.7%)	283 ‡ (76.9%)	76 § (78.4%)	19 (39.6%)	0.5068	**< 0.0001**	**< 0.0001**
No GCs	29 (4.7%)	26 (6.3%)	2 (1.9%)	1 (1.0%)	0.1219	0.0568	**0.9732**
CYC #	487 (78.3%)	355 (85.7%)	88 (83.0%)	44 (43.1%)	0.4801	**< 0.0001**	**< 0.0001**
RTX #	58 (9.3%)	53 (12.8%)	5 (4.7%)	0 (0.0%)	**0.0183**	–	-
MTX #	39 (6.3%)	22 (5.3%)	1 (0.9%)	16 (15.7%)	0.0914	**0.0003**	**0.0003**
AZA #	30 (4.8%)	14 (3.4%)	2 (1.9%)	14 (13.7%)	0.6312	**< 0.0001**	**0.0033**
MMF #	5 (0.8%)	3 (0.7%)	0 (0.0%)	2 (2.0%)	–	0.5637	-
IVIG #	31 (5.0%)	26 (6.3%)	3 (2.8%)	2 (2.0%)	0.2527	0.1386	**0.9653**
Plasmaphereses +	72 (11.7%)	56 (13.8%)	16 (15.1%)	0 (0.0%)	0.7385	–	-

No data in 3 cases of GPA; † 513 cases available for GCs pulses analysis; ‡ 368 cases available for GCs pulses analysis; § 97 cases available for GCs pulses analysis; ¶ 48 cases available for GCs pulses analysis.
+ No data in 12 cases of GPA.
Additionally, 2 cases of GCs use in unknown form, 2 cases of cyclosporine use, 1 case of sulfasalazine use and 1 case of chloroquine use in induction remission.
Assumed statistical significance level of $\chi 2$ test (with Yates correction if needed) = 0.05, adjusted with Bonferroni correction if multiple comparisons performed = 0.017.
Statistically significant p-values are **bolded**.
Abbreviations: GCs = glucocorticoids; CYC = cyclophosphamide; RTX = rituximab; MTX = methotrexate; AZA = azathioprine; MMF = mycophenolate mofetil; IVIG = intravenous immunoglobulins.

Table 3
Renal replacement therapy.

	All	GPA	MPA	EGPA	GPA/MPA * (p-value)
No. of cases (N)	613	405	106	102	–
Haemodialysis (totally)	134 (21.9%)	87 (21.5%)	47 (44.3%)	0 (0.0%)	< **0.0001**
Haemodialysis temporarily	43 (7.0%)	32 (7.9%)	11 (10.4%)	0 (0.0%)	0.4136
Haemodialysis permanently/End stage renal disease	91 (14.8%)	55 (13.6%)	36 (34.0%)	0 (0.0%)	< **0.0001**

Assumed statistical significance level of $\chi 2$ test (with Yates correction if needed) = 0.05.
Comparison was performed only between GPA and MPA group, as there was no case of EGPA who needed renal replacement therapy.
Statistically significant p-values are **bolded**.

3.5. Cumulative immunosuppressive drug doses

The median cumulative dose of cyclophosphamide equalled 7.99 g (4.18–14.0). The highest amount of cyclophosphamide was administered to GPA patients (9.0 g; 5.3–16.0). The median cumulative dose of cyclophosphamide adjusted for a year of observation equalled 2.65 g/year with no statistically significant differences between the subgroups (GPA, MPA, EGPA). There were 46 cases (46/493; 9.33%), in which the cumulative dose of 25 g was exceeded, mainly diagnosed with GPA. The median cumulative dose of rituximab equalled 2000 mg (1500–2800).

More details are available in the Supplementary Table s3 and Supplementary Table s4.

3.6. Differences in AAV patients diagnosed in different time periods

The analysis of AAV group, based on the time of diagnosis was performed. The lowest use of cyclophosphamide as the maintenance treatment was in the group diagnosed after 2010 (20//351; 5.70%), comparing to the group with diagnosis made before 2004 (18/69; 26.09%; $p < 0.0001$) and group diagnosed between 2004 and 2010 (31/195; 15.90%; $p = 0.0001$). The use of azathioprine and methotrexate was also lower in patients diagnosed in the most recent period than in the earlier periods ($p = 0.0004$ and 0.0115 for azathioprine use and methotrexate use, respectively). The details are presented in Fig. 1 and in the Supplementary Table s5. The rate of adverse events as related to the time period when the AAV diagnosis was established is displayed in Fig. 1.

3.7. Adverse events

Adverse events occurred in 377 of AAV patients with infections being the most common. The definitions of adverse events were based mainly on clinical assessment (more detailed information with full list of side effects is provided in the Supplementary Table s6. All mentioned cases of infections in the medical documentation were considered as relevant. Patients who developed infections were characterized by the longer average observation time (median 4.75 years vs. 2.75 years; $p = 0.034$; OR = 1.05; 95% CI 1.00–1.10). Also, they more often received GCs pulses (at least one pulse vs. no pulses; 75.2% vs. 61.7%; $p < 0.001$; OR = 2.83; 95% CI 1.73–4.64) and more frequently needed haemodialysis (29.38% vs. 18.37%; $p = 0.018$; OR = 1.725; 95% CI 1.10–2.71). Cumulative cyclophosphamide dose was not associated with occurrence of infections ($p = 0.092$). The detailed data are presented in Table 5.

3.8. Relapses and mortality

The highest proportion of patients who developed relapses was in the EGPA subgroup. In the analysis, regarding cumulative number of relapses in our AAV population, the association with infections was found ($p = 0.0002$; results obtained using linear regression model). No factors were revealed to be associated with the occurrence of relapses which required hospitalisation. More information concerning relapses is available in Table 1.

There were 56 deaths among all patients with AAV (8.96%). The mortality rate was similar in GPA and MPA groups (10.07% and 12.26%, respectively; $p = 0.5112$), whereas only 1 patient diagnosed with EGPA died (0.98%). Treatment related factors associated with death were: need for haemodialysis ($p < 0.0001$) and steroid pulse use ($p = 0.0425$). The more detailed description of mortality among the cases gathered in the POLVAS retrospective database is presented in another publication [10].

Table 4
Immunosuppressive drugs used among those who received maintenance therapy.

	All	GPA	MPA	EGPA	GPA/MPA (p-value)	GPA/EGPA (p-value)	MPA/EGPA (p-value)
No. of cases (N)	592	402	103	87	–	–	–
GCs	499 (84.3%)	333 (82.8%)	86 (83.5%)	80 (92.0%)	0.8738	0.0333	0.0804
AZA	224 (37.8%)	162 (40.3%)	23 (22.3%)	39 (44.8%)	**0.0007**	0.4363	**0.0010**
MTX	136 (23.0%)	104 (25.9%)	8 (7.8%)	24 (27.6%)	**0.0001**	0.7414	**0.0003**
MMF	99 (16.7%)	74 (18.4%)	16 (15.5%)	9 (10.3%)	0.4965	0.0693	0.2918
CYC	70 (11.8%)	50 (12.4%)	10 (9.7%)	10 (11.5%)	0.4450	0.8078	0.6895
CYA	23 (3.9%)	19 (4.7%)	2 (1.9%)	2 (2.3%)	–	–	–
CLQ and HCQ	11 (1.9%)	7 (1.7%)	0 (0.0%)	4 (4.6%)	–	0.1033	–
RTX	8 (1.4%)	6 (1.5%)	2 (1.9%)	0 (0.0%)	–	–	–
LEF	2 (0.3%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	–	–	–
Other biological agents †	5 (0.8%)	3 (0.7%)	0 (0.0%)	2 (2.3%)	–	–	–
IVIG	9 (1.5%)	8 (2.0%)	1 (1.0%)	0 (0.0%)	–	–	–
No maintenance treatment	36 (6.1%)	28 (7.0%)	6 (5.8%)	2 (2.3%)	0.6804	–	–

† Belimumab, tralokinumab, infliximab.
8 patients (5 with GPA and 3 with MPA) died < 6 months after AAV diagnosis – they were excluded from analysis pertaining maintenance therapy.
Assumed statistical significance level of $\chi 2$ test (with Yates correction if needed) = 0.05, adjusted with Bonferroni correction if multiple comparisons performed = 0.017.
Statistically significant p-values are **bolded**.
Abbreviations: GCs = glucocorticoids; AZA = azathioprine; MTX = methotrexate; MMF = mycophenolate mofetil; CYC = cyclophosphamide; CYA = cyclosporine; CLQ = chloroquine; HCQ = hydroxychloroquine; RTX = rituximab; LEF = leflunomide; IVIG = intravenous immunoglobulins.

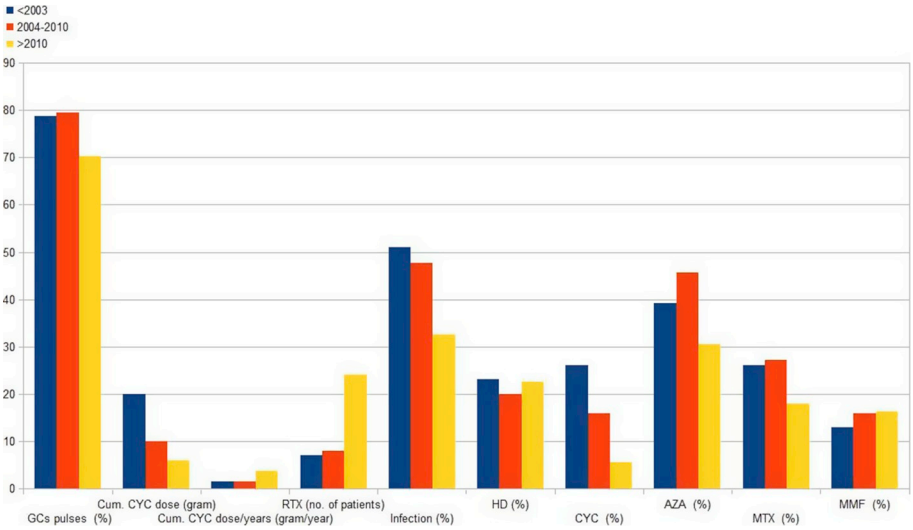

Fig. 1. Differences between chosen factors in AAV patients diagnosed in different periods.
Footnote: Cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil use during maintenance treatment
More detailed information is provided in the article text and in the Supplementary Table s5.
Abbreviations: GCs = glucocorticoids; CYC = cyclophosphamide; RTX = rituximab; AZA = azathioprine; MTX = methotrexate; MMF = mycophenolate mofetil; HD = haemodialysis.

Table 5
Association of chosen factors with infections occurrence.

	p	Odds ratio (exp B)	95% CI (lower border)	95% CI (upper border)
Cumulated CYC dose	0.092	1.012	0.998	1.026
GCs pulses use	**< 0.001**	2.759	1.677	4.536
Observation time	**0.029**	1.053	1.005	1.104
Haemodialysis	**0.018**	1.725	1.098	2.709

Binary logistic regression was used to obtain the results. Assumed level of statistical significance = 0.05.
Statistically significant p-values are **bolded**.
Abbreviations: CYC = cyclophosphamide; GCs = glucocorticoids.

4. Discussion

Based on the POLVAS registry database, we characterised the treatment of AAV in Poland. Demographic characteristics of described population did not vary considerably comparing to the populations in similar studies [11–15]. Generally, AAV therapy was consistent with recently published guidelines [16,17]. Of note, 6.1% of patients in our study did not receive any maintenance treatment, after exclusion of patients who had died before starting maintenance therapy. However, it might be a result of a short follow up in cases still being in an induction phase of remission by the time of recording their data in the registry. The median cumulative dose of cyclophosphamide amounted to 7.99 g, and does not exceed suggested whole-life dose of 25 g [17]. However, 9.33% of registered population received doses greater than 25 g. Cumulative doses of cyclophosphamide in our study were lower than those reported in patients before publication of CYCAZAREM [7] and CYCLOPS [18,19] results and comparable to or even lower than doses reported in later studies [11,20–23]. In the vast majority of cases GCs were used permanently during the whole observation time, probably due to predominance of cases with rather short observation time. Alternatively, it might show the tendency to prolong maintenance therapy with systemic GCs. Due to frequent adverse events associated with such treatment much shorter periods of steroid therapy are now suggested in the AAV patients [16,17,24].

There were some significant differences in the way AAV patients were treated depending on the clinical diagnosis. GCs were frequently the only agents used for induction of remission in EGPA patients, consistent with former guidelines to use steroid monotherapy in less severe cases [25,26]. However, according to newer data, concomitant use of GCs together with an additional immunosuppressive drug is suggested for all EGPA cases [27,28].More frequent use of methotrexate and azathioprine, less frequent use of cyclophosphamide as well as GCs pulses and no use of rituximab or plasmaphereses - these differences may reflect less severe course of EGPA, comparing to the other AAV entities. However, due to the lack of the Birmingham Vasculitis Activity Score (BVAS) and Five Factor Score (FFS) such assumption could not be definitely supported. Patients with MPA required haemodialysis significantly more frequently than GPA patients. This is consistent with other reports showing that diagnosis of MPA and anti-myeloperoxidase antibodies (anti-MPO) positivity are associated with severe renal involvement [29,30]. Cumulative dose of cyclophosphamide was higher in GPA comparing to MPA, which may be due to the higher tendency to relapse in anti-proteinase 3 antibodies (anti-PR3) positive cases [31,32]. However, it might be also influenced by shorter observational time in MPA group, as adjustment of cumulative dose of cyclophosphamide for the length of observation showed similar cumulative dose of cyclophosphamide per year of observation. We also noticed a relatively high number of MPA patients treated with GCs alone for induction remission (14.2%). As the trials in which such treatment regimen was administered showed unfavourable outcomes [33,34], and according to the current recommendations [16], such treatment should be abandoned.

Relatively less frequent use of rituximab in our AAV patients for induction of remission in severe disease exacerbation was mainly due to the lack of drug cost reimbursement program in our country at the time of data collection. Such refunding policy started by the end of 2016 which will allow for comparison between recently recommended remission induction regimens by cyclophosphamide or rituximab [16] in a prospective arm of the POLVAS study. We also found, that renal recovery after the time of temporary renal replacement therapy was associated with lower age. Moreover, the results for possible correlation of cyclophosphamide as well as plasmaphereses use with renal recovery - the factors reported to be associated with better renal outcomes by others - were near the threshold of statistical significance in our analysis [35–37]. Adverse events assumed to be related to the treatment were relatively common in the studied cohort.

Not surprisingly, the most frequently seen treatment side effects were infections (38.8% of all cases) - similarly to the other reports (range of infectious complications 26–39.9%) [11,15,38–40]. The factors associated with higher proportion of cases with infectious adverse events were time of observation, GCs pulses use and need for renal replacement therapy. The GCs pulses use might be the reflection of more intensive treatment and the higher total dose of GCs, which was associated with higher risk of infections in the other papers [15,41]. Three subgroups, differed by the time of diagnosis showed some interesting differences. Patients diagnosed in the earlier periods received

higher median cumulative doses of cyclophosphamide. Also, higher proportion of them developed infectious adverse events during follow up – an observation already made by the other authors [15]. The proportion of cases who developed infections was the lowest in the group with diagnosis of AAV established after 2010, comparing to the groups diagnosed in the earlier periods. It may be a reflection of changes in the maintenance therapy over time with replacement of cyclophosphamide by methotrexate, azathioprine or mycophenolate mofetil. On the contrary, it could also be associated with the shorter time of observation in this group. Interestingly, patients with diagnosis made after 2010 had significantly higher median dose of cyclophosphamide per year. It could be associated with the number of patients who were during or just after induction remission treatment in their first year of observation. A remarkable decrease in cyclophosphamide use as maintenance therapy was seen after CYCAZAREM, than RAVE and RITUXVAS [7–9] publications, which reflected the change in recommendations to rather use other agents than cyclophosphamide for this phase of treatment. Treatment-related factors associated with death were: need for haemodialysis which represents patients with severe renal involvement – the known factor of poor outcome in AVV [11,42], and steroid pulses use, which may indicate the group with more severe onset or further course of the disease. The cumulative number of relapses was associated with infection occurrence which could be a reflection of more intensive treatment, required during exacerbations of disease, which in turn may result in higher risk of infectious complications. The high prevalence of relapses in EGPA group was probably the result of assuming asthma exacerbations as relapses – such statement was made in another paper based on the data from the POLVAS population [7].

The main strength of our study is the number of cases included, which is the largest description of treatment strategies in AAV in Poland, and one of the largest ever reported.

On the contrary, there are also several drawbacks of this research. First of all, the data were collected retrospectively which may have led to some inconsistencies, errors and lacks of data. The significant shortage of data concerns especially the area of treatment related complications, which reaches about 50% of cases in some groups. Due to the difficulties in obtaining all necessary data, BVAS, Vasculitis Damage Index (VDI) and FFS indices were not assessed in the retrospective part of the database, so the objective judgment on cases severity is limited. Because of the retrospective character of data collection, the definitions of adverse events used in the registry are generally simplified, which may cause difficulties in detailed interpretation. Additionally, the number of adverse events and their severity was unknown. Relatively short time of observation may be considered as another limitation when analysing the cumulative dose of drugs used. The adjustment of the dose of immunosuppressant for a year of observation could partially overcome this limitation. The data from retrospective part of the database do not include also the information on the cumulative doses of GCs, which does not allow to analyse the overall steroid use. Furthermore, there are no data regarding the time to the occurrence of the analysed events, which makes it impossible to conduct the time-to-event analysis. Some adverse events of immunosuppression, such as neoplasms, may develop over longer period of time [43,44]. Therefore, their proportion might be underestimated in this study. Prospective cohort analysis may overcome aforementioned limitations in the future.

5. Conclusions

The treatment regimens and associated side effects among Polish AAV population described in retrospective branch of POLVAS registry seem to be similar to the other reports. Some differences in treatment between specific AAV entities were found – especially EGPA patients were treated less aggressively than those with MPA or GPA. Our analysis indicated the tendency to limit the cyclophosphamide in newer cases, especially in maintenance therapy. Lower rituximab administration was associated with no refunding policy to the end of 2016 year. The development of infections, which were the most frequent adverse effects of treatment, was related with GCs pulses use, time of observation and need for haemodialysis, but not with cumulative dose of cyclophosphamide.

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DATA statement

We claim that the submitted article is based on the data collected in the POLVAS Registry (Consortium of the Polish Vasculitis Registry) - Musial J, Wojcik K. Polish Vasculitis Registry: POLVAS. Pol Arch Intern Med. 2017; 127 (1):71-2.

Due to the extensive size of these data, we do not attach them to the manuscript.

We claim that we are authorized to use the data collected in the POLVAS databases by the POLVAS Steering Committee.

Declaration of competing interest

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.advms.2020.01.002.

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